IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	Bryan John Smith	
APPLICATION NO.	:	09/831,534	EXAMINER : Dibrino, Marianne Nmn
FILED	:	June 18, 2001	ART UNIT : 1644
FOR	:	ANTIBODY-SERUM PROTEIN HYBRIDS	

DECLARATION OF BRYAN JOHN SMITH, PhD. UNDER 37 C.F.R § 1.132

Dear Sir:

I, Bryan J. Smith, Ph.D. hereby declare and state that:

1. I am Associate Director, Protein Chemistry in the BioProcess Research Department of UCB (formerly Celltech Therapeutics Limited) located at 208 Bath Road, Slough, United Kingdom. I have worked on protein research at Celltech/UCB since 1984 and have held my current position since 1998. I have published extensively on the subject of protein chemistry (about 80 papers, book chapters and posters) including, for example, Smith *et al.,* Prolonged *in vivo* residence times of antibody fragments associated with albumin, 2001, Bioconjugate Chemistry, 12, 750-756.

2. I have read and am familiar with United States Patent Application 09/831,534 for which I am listed as the sole inventor.

3. The present invention provides an antibody-albumin conjugate in which the antibody fragment is site-specifically bound via a linker of 10-20Å in length to a single cysteine at position 34 of albumin.

4. Site-specific conjugation ensures that the conjugates produced are homogeneous and thus suitable for therapeutic use. This is in contrast to random conjugation where the sites of attachment can vary each time the conjugate is produced.

5. The conjugates of the present invention can be produced efficiently. In particular, by using a linker of 10-20Å in length albumin homodimers are not formed and all the albumin molecules with linkers attached are available for conjugation to an antibody fragment. If homodimers were formed these would have to be purified away from the final conjugate, thus reducing efficiency and increasing the cost of production.

6. The present invention represents a whole new approach to albumin conjugation. Thus, there were a number of technical questions which could only be answered experimentally. Accordingly, at the time the invention was made I did not know whether it would be possible to conjugate an antibody fragment site specifically via a linker to cys 34 of albumin. Even if that were possible, I did not know what effect this would have on antigen binding, albumin conformation and conjugate half-life.

A. Linker length and composition

7. The cysteine at position 34 of albumin had never previously been used as a site of attachment for an antibody fragment. Therefore, it was not known what length or composition of linker would be effective.

8. From the crystal structure of albumin it was known that cys 34 is buried in a groove between two helices. This suggested that the cysteine might not be readily accessible to bind a linker. Further, it was not possible to predict how long a linker would be needed to work effectively because the crystal structure does not show how the albumin and the linker behave in solution. Before the present invention, I could not predict whether the linker I had selected would work.

9. There were a number of technical questions about the linker that had to be tested experimentally including the following:

(i) Whether the linker would be long enough to reach the antibody fragment?

(ii) Whether the linker would also be short enough not to reach another cys 34 in another albumin molecule, i.e. to avoid the formation of albumin homodimers?

(iii) Whether the linker would be available to bind to the antibody fragment? It was possible that the linker might bind non-covalently to albumin, e.g. within the groove, and therefore not be available for binding to the antibody fragment.

B. Effect of conjugation on antigen binding and albumin half-life

(1) Antigen binding

10. Before the subject invention was made, I could not predict whether the antibody fragment would still be capable of binding to its antigen once albumin was attached to the fragment via the linker. There were a number of reasons why antigen binding might have been affected including the following:

(i) Albumin is known to non-specifically bind to certain proteins and other molecules. It was possible that the albumin would bind to the antibody fragment and interfere with antigen binding, for example by altering the conformation of the antibody fragment.

(ii) The antibody Fab' and $F(ab')_2$ fragments in the examples comprise an antibody hinge region to which the albumin molecule is site specifically attached via the linker. The antibody hinge region is known to be flexible and so it was possible that the albumin could swing around to the antigen binding site and interfere with antigen binding, either directly by binding to the antigen binding site or indirectly for example by binding to the antigen.

(iii) It was possible that the mere presence of the albumin and linker attached to the antibody fragment, in particular given the large size of albumin (67kDa), could affect the conformation of the antibody fragment and accordingly antigen binding.

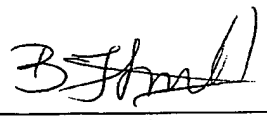
(2) Albumin half life

11. The cysteine at position 34 of albumin is known from the crystal structure to be buried in a groove between two helices. As this was the first attempt to conjugate an antibody fragment to this cysteine I could not predict beforehand what effect this would have on the structure of the albumin and consequently what effect this would have on the half-life of the albumin-antibody conjugate.

12. I have reviewed United States Patent 5,714,142 and WO 98/00717. I understand that the Examiner maintains that it would have been obvious to use the linkers disclosed in these patents to link an antibody to albumin at the cysteine at position 34. The linkers disclosed in United States Patent 5,714,142 and WO 98/00717 were not used to site specifically link the drugs described to albumin at position 34. Accordingly, it would not have been possible to predict whether the linkers described would be suitable for site-specific conjugation of an antibody fragment to albumin at position 34.

13. The linkers described in United States Patent 5,714,142 and WO 98/00717 are part of the structure of the drug. That is, the albumin is conjugated to the linker which is already attached to the drug, not vice versa. It would have been impossible to predict whether the same linker once attached to albumin would be incapable of forming homodimers with another albumin molecule.

14. I declare further that statements make in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.



Bryan J. Smith, Ph.D.